REMARKS

Applicant has corrected the listing of Claims to make them compliant with the Revised Amendment Practice, as described in the 7/24/03 (rev 3.), which was mandatory as of July 30, 2003.

Applicant's Specification contemplates immunotherapeutic methods for treating prostate cancer using an immunoconjugate comprising PROST 03 antibodies and toxic agents. Claims 28 and 29 are currently pending in this application, having been elected by the Applicant in response to a Restriction Requirement (paper 6, mailed May 7, 2002). Reconsideration of this application is respectfully requested.

Rejection under 35 USC §112, first paragraph

The Examiner has rejected Claims 28 and 29 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the Specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

On pages 2-6 of the Office Action, the Examiner goes to great lengths to provide examples, some relevant and some irrelevant, to support her contention that the state of the art in this technical field is so highly unpredictable that Applicant must provide examples of *in vivo* killing of a cell expressing SEQ ID NO: 2 or treating prostate cancer in the Specification in order to be enabling. Applicant strongly disagrees.

It is clear from the Specification that PROST 03 is significantly expressed in prostate-derived tissues **only**, and is over-expressed in prostate tumors (see pg 43, Example 5). Accordingly, Applicants contend that given the tumor-specificity of the PROST 03 (SEQ ID NO: 2) target, and the known ability of immunoconjugates to bind specifically to antigens targeted by an appropriate monoclonal antibody, it would be reasonable to one skilled in the art to assume that an immunoconjugate targeted to PROST 03 would be useful in treating prostate cancer, as well as metastasis of such cancer.

The PTO has indicated that *in vivo* data is not necessary to support utility (see *In re Brana*, 51 F .3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995). Applicants have demonstated the prostate-specific nature of the target and the ability to generate monoclonal antibodies to said target, and accordingly contend that one skilled in the art would clearly recognize the potential utility of such targeted monoclonal antibodies. Moreover, at the time the invention was made, there were many examples of immunoconjugates comprising antibodies and toxins being used to selectively kill cells (see, for example, USP 5,863,745; USP 6,099,842; Liu et al., "Eradication of large colon tumor xenografts by targeted delivery of maytansinoids" *Proc. Natl. Acad. Sci. U.S.A,* Vol. 93, 8618-8623 (1996), and Bera, et al., "Bivalent Disulfide-stabilized Fragment Variable Immunotoxin Directed against Mesotheliomas and Ovarian Cancer," *Mol. Cancer Therapeutics*, Vol 1, 79-84 (2001), copies of which are attached for your review).

The Examiner has contended that "it was well known in the art at the time the invention was made that although immunotoxins were highly effective as a means of selectively targeting cancer cells, immunotoxins have proved relatively ineffective in the treatment of solid tumors such as carcinomas". The evidence the Examiner provides is a patent application, published in 1993, which is directed toward "antibodies carrying diagnostic or therapeutic agents targeted to the vasculature of solid tumor masses through recognition of tumor vasculature-associated antigens" (see Abstract of WO93/17715). The application also states "Thus, it is quite clear that a significant need exists for the development of novel strategies for the treatment of solid tumors. *One approach* would be to target cytotoxic agents or coagulants to the vasculature of the tumor rather than to the tumor." It it certainly not surprising that in a patent application seeking to show the novelity and potential utility of *the approach* for which a patent is being sought, the inventors would point out the problems which **could** arise with other methodologies in use at the time (some 7 years prior to the filing date of the instant application). On page 6 of WO93/17715, it states "The invention rests...on the use of immunological reagents to target therapeutic or diagnostic agents to tumor-associated vasular endothelial cells.....". Applicants contend that these are the very same principles upon which the claimed invention rests, only with the use of a different target.

The Examiner cites the article by White et al. which indicates that several other issues, beside the specificity of the antigen, must be considered in the use of immunotherapy. An article by Gutheil, *Critical Reviews in Oncology /Hematology*, 38: 1-2 (2001), summarizes approaches which can be taken to address these issues, clearly indicating that those skilled in the art at the time of the instant invention were aware of these concerns. Applicants argue that it would be normal during the process of drug development to refine the use of the therapeutic candidate and that one skilled in the art had the knowledge to realize the therapeutic usefulness of the claimed invention

The Examiner has also argued that one can not extrapolate the teaching of the Specification to the claims because it is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable. In order to support this contention, she cites a general article from 1997 relating to the number of potential anticancer agents which have been sifted through over the years, with only a small number finally showing use in chemotherapy.

The title of the article is "Systems for Identifying New Drugs are Often Faulty" and the focus of the article is a description of problems with various methods for screening of potential cancer therapeutics. The conclusion of the article is that "cancer drug screening is turning almost exclusively toward defining molecular targets". The instant invention is a therapeutic immunoconjugate which has a defined molecular target. It can be screened using prostate cancer cells and prostate-derived xenografts. Clearly the issues raised by this article regarding appropriate screens are not relevant.

The Examiner then cites another general article (Sci. Am., 1994, 271: 58-65) that teaches that tumors resist penetration by drugs. Applicants, however, point out that an immunoconjugate does not necessarily require that a cell be penetrated by a drug; i.e. if the immunoconjugate contains a radioactive moiety, the radioactivity can act within a certain range to kill cells.

The Examiner next cites Hartwell et al. (Science , 1997, 278:1064-1068) as teaching that the chemotherapeutic agent must selectively kill tumor cells and that systemic treatment typically consists of chemotherapeutic drugs that are toxic to dividing cells. Applicants point out that Examiner's concern is not an issue in this case since the

main advantage of the use of immunoconjugates, including the ones claimed herein, is that they are targeted. Therefore, the PROST 03 immunoconjugate claimed herein is useful because the prostate-specific nature of the antigen portion of the immunoconjugate directs the immunoconjugate to the cells that need to be destroyed, thus limiting any undesirable cytotoxicity.

The Examiner's final paragraph relates to the unpredicatability of immunotherapy, i.e. cancer vaccines. Given that there are no claims directed to "cancer vaccines" currently pending in the application, Applicants do not see how these arguments relate in any way to the claims currently being reviewed.

In view of the foregoing, Applicants request that the Examiner reconsider her rejection of the claims under Section 112, first paragraph.

Rejection under 35 USC §112, first paragraph

The Examiner has rejected Claim 28 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for selectively killing a prostate cancer cell expressing SEQ ID NO: 2, does not reasonable provide enablement for a method for selectively killing of a cell expressing SEQ ID NO: 2.

Claim 28, as amended herewith, claims a method for selectively killing a prostate-derived cell, and Applicants believe this claim, as the Examiner has stated, is enabled.

The Examiner also rejects Claims 28 and 29 under 35 U.S.C. 112, first paragraph, because the specification, is not enabling for selectively destroying a cell expressing SEQ ID NO: 2, or a method of treating prostate cancer, comprising administering an immunoconjugate of "a monoclonal antibody" or fragment thereof, which specifically binds to "one or more epitopes" of SEQ ID NO: 2. As the Examiner has correctly pointed out, a monoclonal antibody is expected to only bind to one epitope. Claims 28 and 29 have been amended herewith to remove language relating to "one or more epitopes" and replace it with "an epitope". Applicants believe that this amendment renders the rejection mute.

Conclusion:

Applicants respectfully submit that with the submission of the newly amended Claims 28 and 29 and the arguments presented above, the application is now in condition for allowance. Such action is solicited at an early date.

Respectfully submitted,

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Date: Sept. 16, 2003